PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Halogen-Substituted Amidoximes and Manufacturing process

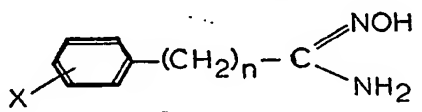
We, A. WASSERMANN S.P.A., SOCIETA ITALIANA PER SPECIALITA FARMACO-TERAPEUTICHE, an Italian Joint Stock Company, of 56, via Andrea Maria Ampere, Milan, Italy, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

Benzamidoximes substituted by a halogen atom in their nucleus, more particularly *o*-chloro-, *m*-chloro- and *p*-chloro-benzamidoxime are known from literature (Werner & Bloch, Ber. *32*, 1979 (1899); Andrews, King & Walker, Proc. Roy. Soc. *133 B*, 20 (1946); Clarke, J. Chem. Soc. *1954*, 4251).

They are prepared by interaction of their corresponding benzonitrile and hydroxylamine hydrochloride in the presence of a base, or by reacting benzhydroxamic chloride and liquid ammonia.

It is moreover known that some alkylene-diamidoximes and benzamidoximes are of antitrypanosomic (Lamb & White, J. Chem. Soc. *1930*, 1253) and antirickettish activity (Andrews, King & Walker, Proc. Roy. Soc. *133 B*, 20 (1946)).

Novel amidoximes of the above referred type have now been found, which are of valuable pharmacological activity. The novel compounds according to this invention comprise phenyl-alkyl-amidoximes in which a halogen atom is substituted in the nucleus, of the following general formula:



wherein *n* is an integer between 1 and 4 inclusive, X being a halogen atom.

The invention concerns more particularly α - phenylacetamidoxime, β - phenyl - propionamidoxime, γ-phenylbutyramidoxime and δ-phenyl-valeroamidoxime, all of them being substituted in their nucleus in accordance with the above general formula. The halogen may be chlorine, bromine, iodine or fluorine.

The invention further provides a method of preparing the above phenyl-alkyl-amidoximes, comprising the step of reacting a corresponding halogen-phenylalkylcyanide (nitrile) with hydroxylamine hydrochloride or other hydroxylamine salt in the presence of a base in an aqueous or alcoholic or alcoholic-aqueous medium. The base is preferably selected among alkali metal alcoholates, alkali and alkaline earth metal carbonates and bicarbonates and pyridine without, however, omitting other suitable bases. The halogen-substituted phenyl-alkyl-amidoxime resulting from the above reaction can be isolated as such or in the form of a soluble salt, such as hydrochloride or hydrobromide.

The starting nitriles employed by the method are known in part from literature. Isomeric β - (*o* - bromo - phenyl) - propionitriles as well as halogen-phenyl-butyronitriles and halogen-phenyl-valeronitriles can, however, be prepared along usual general processes, such as by distilling their respective amides with phosphoric anhydride, thionyl chloride and phosphorus pentachloride, or by cyaniding their corresponding halogen-derivatives by an alkali metal cyanide.

Halogen - substituted phenyl - alkyl-amidoximes according to this invention exhibit an unexpectedly marked hypotensive

action, which is of an appreciably lasting character, in a fairly small dose. The therapeutical index of these amidoximes decidedly recommends them for pharmacotherapeutic use.

The processes of preparing α-(*o*-bromophenyl)-acetamidoxime and β-(*o*-bromophenyl)-propionamidoxime.

Example 1: 26 gr *o*-bromo-benzylcyanide and 9.25 gr hydroxylamine hydrochloride are added to a solution of 3 gr sodium in 250 ml absolute ethanol, the whole being reflux-boiled over a water-bath during two hours and cooled. Separated inorganic salts are filtered off. The filtrate is cooled by means of a refrigerating mixture, yielding a precipitate of *o*-bromo-phenylacetamide which is removed by filtering. This product is known from literature, its melting point being 186—187° C.

The alcoholic mother-liquors are evaporated by vacuum distillation (water pump) to a volume of 75 ml, thereupon acidified to pH = 4. The unreacted starting product is extracted by ether, the aqueous solution being neutralised by means of an alkali metal bicarbonate till full precipitation of *o*-bromo-phenylacetamidoxime, which is isolated by filtering and crystallising from ethanol and isopropyl ether. Output 15 gr; melting point 128—130° C.

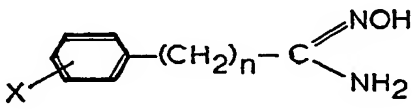
Upon recrystallising from a mixture of ethanol and isopropyl ether the hydrochloride of this amidoxime is in the form of colorless non-hygroscopic glossy scales which melt at 147—149° C.

Example 2: 19 g *o*-bromo-phenylpropionamide (Gonzales, Anales fis. y quim. *40*, 1182, (1944) are reflux-heated over a direct flame during an hour and a half with 20 ml thionyl chloride, while they are protected against moisture by means of a $CaCl_2$ tube, whereupon the mixture is concentrated to a small volume and the residue is taken up with ethyl alcohol. The ethereal solution is washed with an alkali carbonate, then distilled in vacuum while it is protected against moisture. This yields 14 g *o*-bromo-phenyl-propionitrile, boiling point 149—151° C at 2 mm mercury column.

14 g of the above nitrile and 5 g hydroxylamine hydrochloride are dissolved in 150 ml absolute ethanol and reflux-boiled during two hours, maintaining the pH of the solution at a constantly neutral value by repeated additions of sodium bicarbonate. The method is henceforth carried out substantially as described in Example 1, by cooling the reaction mixture, removing inorganic salts, etc. This yields 10 g *o* - bromo - phenyl - propionamidoxime, melting point 109—110° C. Upon recrystallising from a mixture of ethanol and isopropyl ether the hydrochloride is in the form of glossy scales and melts and decomposes at 180—182° C.

WHAT WE CLAIM IS:—

1. Halogen-phenyl-alkylamidoximes of the following general formula:



wherein *n* is an integer between 1 and 4 inclusive, X being a halogen atom.

2. Halogen - phenyl - alkylamidoximes as claimed in Claim 1, comprising α-phenyl-acetamidoximes halogen-substituted in the nucleus.

3. Halogen - phenyl - alkylamidoximes as claimed in Claim 1, comprising β-phenyl-propionamidoximes halogen-substituted in the nucleus.

4. Halogen - phenyl - alkylamidoximes as claimed in Claim 1, comprising γ-phenyl-butyramidoximes halogen-substituted in the nucleus.

5. Halogen - phenyl - alkylamidoximes as claimed in Claim 1, comprising δ-phenyl-valeroamidoximes halogen-substituted in the nucleus.

6. Method of preparing a halogen-phenyl-alkylamidoxime as claimed in Claim 1, comprising the step of reacting a corresponding halogen-phenyl-alkylcyanide with hydroxylamine hydrochloride or other hydroxylamine salt in the presence of a base in an aqueous or alcoholic or alcoholic-aqueous medium.

7. Method as claimed in Claim 6, in which the base is selected from the group comprising alkali metal alcoholates, alkali and alkaline earth metal carbonates and bicarbonate and pyridine.

8. Method of preparing a halogen-phenyl-alkylamidoxime as claimed in Claim 1, substantially as described in Example 1 or 2 herein.

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